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The future of pharmaceutical manufacturing in the context of the scientific, social, technological and economic evolution

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ABSTRACT

Healthcare provision is one of the import elements of modern societies. Life sciences and technology has made substantial progress over the past century and is continuing to evolve exponentially in many different areas. The use of genotypic and phenotypic information in drug discovery and drug therapy, the increasing wealth around the world, growing patient involvement through information and communication technology and finally innovations in pharmaceutical manufacturing technology are transforming the provision of healthcare. The adoption of this new science and technology is going to happen due to the synergistic effects and visible benefits for the society and healthcare systems. The different aspects driving advanced pharmaceutical manufacturing are reviewed to identify future research direction to assure overall acceptance and adoption into healthcare practice.

1. Introduction

The provision of effective healthcare is an essential contributor to the wealth of any society around the world and a fundamental basis for the future prosperity. Healthcare is generally provided through a variety of different interventions to prevent, treat or manage diseases or injuries of the individual. Substantial progress have being made during the past centuries in medical and pharmaceutical sciences with some of the most important disruptive innovations occurring just during the past five decades. This has led to a continuously increasing importance of medicinal products in the treatment and management of acute and chronic diseases and hence the provision of effective healthcare to patients. The way how these medicinal products are discovered, developed, manufactured, distributed and used is happening within the context of several scientific, technological as well as social, economical and political dynamics. To predict the research needs and directions of pharmaceutical manufacturing in the coming decades, it is critical to understand the context and the potential impact of ongoing dynamics in the areas affecting the healthcare provision. This review is intended to look into the dynamics and advances in the most relevant areas of medicinal product manufacturing and attempts to give some predictions about medicinal products and their manufacturing in the coming decade.

2. The context of pharmaceutical manufacturing in healthcare provision

Drug product discovery, development and manufacturing is a science and technology driven area that has and continues to evolve constantly. This progress has led to the introduction of more than 600 new drugs over the past 20 years. Healthcare professionals prescribe these medicinal products to patients suffering from a disease for which the medicinal product is effective. To achieve this objective, medicinal products have to be developed, manufactured and documented according to regulatory guidelines in order to consistently prove and meet quality, safety and efficacy [Morrison, 2000].

The provision of healthcare and especially healthcare products and services is incremental to our daily live and part of the society's responsibility. Advances and innovations in healthcare occur simultaneously in different domains. Some advances are developed synergistically; others are develop in parallel, but come together at a certain point in the healthcare delivery chain. The scientific domain includes the progress in medical sciences through systems biology, systems medicines and the use of genomic information in drug discovery and clinical practice tailoring drug therapy to the individual patient. The society domain and social dimension is driven by the increasing availability, access and use of healthcare information in personal drug therapy decision making. The personal involvement in the own health is further supported by the increasing application of Information and Communication Technology (ICT) that includes the constant and in situ gathering of biometric data. Another important domain affecting future healthcare provision is the demographic shift and aging society creating patient populations that are characterized by very high age, multimorbidity, polypharmacy and frailty. Pharmaceutical manufacturing is developing by itself through enhanced and enabling technology moving the traditional batch based processes towards continuous manufacturing and highly flexible advanced manufacturing. Implementation of Process Analytical Technology (PAT) and digital data processing allow for close

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loop quality control systems and real time release. As several of the advancements and innovations being made in the different domains must be considered as disruptive innovation, the acceptance, adoption and implementation into the future healthcare provision will remain a challenge. The critical demonstration of its value and benefit for the individual as well as the society and the healthcare system is ongoing providing the basis for its future integration. This prediction of the future pharmaceutical manufacturing is based on a critical review of these developments in the different domains and the expected impact on the provision of the future healthcare in developed as well as developing countries.

2.1. Scientific and medical domain

Drug discovery is an essential part in the provision of new drug products to treat or manage acute and chronic diseases more efficiently as well as the very complex life threatening diseases. With the introduction of combinatorial chemistry and high throughput screening in the mid 1990s, drug discovery took a big step forward to a more rational receptor or target based drug design. As a result, the drug properties shifted towards higher molecular weight and lipophilicity requiring additional drug delivery technologies to develop the drug into a viable drug product [Lipinski et al., 1997, Lipinski, 2000]. Biotechnological advances provided a new avenue into the discovery and development of biological compounds like proteins, monoclonal antibodies (Mabs) and siRNAs creating a new kind of targeted and personalized therapeutics [Walsh, 2010]. A lot of emphasize, efforts and expectations were attributed to the sequencing of the human genome as the important step forward in medicinal therapy [Collins, 1999]. The sequencing of the human genome was finalized in the beginning of the century [International Human Genome Sequencing Consortium, 2001; International Human Genome Sequencing Consortium, 2004], however anticipated break through by the application of bioinformatics to the genomic information to fully understand the root causes of the disease and develop drugs against the new targets did not occur. The results were very disappointing [Kubinyi, 2003], mainly because the normal gene variation between humans affect about 1–2% of the genomic sequence including 3.5 million Single Nucleotide Polymorphism (SNP), 1 million micro-deletions, −duplications or –insertions, 20.000 copy number variants, 9.000–11.000 variants in protein coding sequences gene variation [Meyer et al., 2013]. During the past decade the costs and time for the sequencing of a complete human genome reached between USD 4.000 – 5.000 within a few days [www.genome.gov/sequencingcosts] and the Food and Drug Administration (FDA) approved the first high-throughput (next-generation) genomic sequencer, Illumina's MiSeqDx in 2013 [Collins and Hamburg, 2013]. This development made human genome sequencing a standardized and affordable tool for routine drug research and diagnostic use. The genome data that are gathered from patients around the world are shared across different consortia correlating the whole genome sets with specific diseases to identify the relevant genomic variants. For example, a genome-wide association study (GWAS) for Parkinson disease was performed using a set of 5.353 Parkinson patients and 5.551 non-Parkinson controls identified 28 independent risk variants across 24 loci and 6 loci that were associated with proximal gene expression or DNA methylation (Nalls et al., 2014]. Linking the phenotype with the genotype as well as environmental patient factors will reveal a mechanistic understanding of a disease and network of diseases with direct impact on the classification of the diseases as well therapy of a patient [Gustafsson et al., 2014; Denny et al., 2013]. As a result of the continuous progress of systems biology and systems medicine, pharmacogenomics data are increasingly required by regulatory authorities [Goodsaid and Frueh, 2007] and became mandatory in indications like oncology [Boulton and Dally, 2010].

Beside the use of pharmacogenomics data in drug selection and targeted disease treatment, pharmacogenomics information are widely used in drug dosing and prevention of adverse drug reaction (Shastry, 2006; Sirot et al., 2006). Taking into account the deceasing cost of the human genome sequencing, we can expect that genomic data will become part of the standard diagnosis of patients in routine primary care settings. Even though genetic biomarker data are mainly used today for the complex life threatening diseases like cancer and inflammatory diseases, their application might quickly be implemented into the treatment of the most common chronic diseases. For example, one of the critical adverse drug reactions of statins is the induction of myopathy in patient population with certain genetic variants affection pharmacokinetic parameter. Identifying these patients early on will prevent patients at risk to develop myopathy as an adverse drug reaction [Talameh and Kitzmiller, 2014]. Economical concerns regarding the broad application of pharmacogenetic testing in drug therapy will have to be evaluated for each specific case, but declining costs of pharmacogenetic tools and advanced in translational sciences are expected to demonstrate its cost efficiency very quickly (Phillips and Van Bebber, 2005).

2.2. Society domain and social dimension

According to the 'survival of the fittest' theory of Darwin, nature has produced a significant number of different species around the world, able to survive under a variety of conditions [Von Sydon, 2014]. Humankind has differentiated from the other animals through the development of higher brain functions, improved diet and intelligence [Kaplan et al., 2000]. This enabled human beings to develop and make use of technology constantly increasing the wealth and independence from Mother Nature. As one of the only species on earth, the life expectancy has grown in humans over the past thousands of years from about 30 years to around 80 years in our days, whereby calculations have been made that the human race would require only 50–55 years of lifetime to reproduce itself according to the Darwin theory [Carnes and Witten, 2014].

With the growing intelligence of humans, science and culture developed across several areas along with the growing wealth. In 1943, Maslow proposed a model on the hierarchy of needs (Fig. 1) that differentiates between 5 different levels of needs, starting from the fulfillment of the basic physiological needs, to safety, social, esteem and finally the desire of self-actualization [Maslow, 1943]. It is obvious that the economic and political development of a country and its society is a major driver to fulfill the elementary needs of the first three level (physiological, safety and social level) and allow people to enter into the development of the personal self, the level of esteem and self-actualization. With the economic growth and peace that the Western World has maintained over the past 70 years in the same way as it is happening in the fast growing and emerging economies over the past decades, the number of people reaching the level of the personal self are becoming significantly bigger every year´ and hence their involvement in the personal health. This doesn't mean that humans and the society judge technology uncritically. Acceptance and implementation of new technology and innovation is going through a process in order to demonstrate its relative value compared to the potential risks [Attridge, 2006; Venkatesh and Davis, 2000]. The same applies to acceptability of information technology and the implementation by individuals and organizations [Lee et al., 2003]. Nevertheless, technology and its adoption into the consumer and healthcare industry occurred very fast in modern societies especially as more and more people get access to economic and societal resources around the world.

2.3. Patient involvement

Involvement into the own health and decision making about therapeutic intervention in case of disease occurrence require medical and pharmaceutical knowledge. This is even more important in the growing complexity of healthcare and therapeutic options. Over many year the relationship between physicians and patients were mainly a directive